Blood pressure, heart rate, and mortality in chronic obstructive pulmonary disease: the SUMMIT trial

Prognostic Importance of Blood Pressure and Heart Rate in Chronic Obstructive Pulmonary Disease: The SUMMIT Trial

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Key Points

Question: Do easily-obtained hemodynamic metrics predict outcomes in patients with COPD and cardiovascular disease or high risk for cardiovascular events?

Findings: In a randomized controlled trial, all-cause mortality increased in relation to high or low systolic or diastolic blood pressure. Higher heart rates and pulse pressures were linearly-related to increases in all-cause mortality.

Meaning: In COPD patients at risk for cardiovascular disease, unusual hemodynamic values portend a worse outcome and may warrant increased clinical vigilance.

Abstract

Importance: Cardiovascular disease is the leading cause of death in patients with chronic obstructive pulmonary disease (COPD). While general associations between high blood pressure (BP) and cardiovascular risk are well-established, their prognostic importance in patients with COPD remains poorly described.

Objective: To characterize the nature of the relationship between BP and heart rate with mortality and morbidity in COPD.

Design: Post-hoc analysis of the associations between baseline BP and heart rate with all-cause mortality and cardiovascular events in the SUMMIT trial.

Setting: A randomized double-blind outcome trial of 16,485 participants enrolled at 1,368 sites in 46 countries.

Participants: Patients with moderate COPD with or at-risk for cardiovascular disease.

Interventions: Patients were randomized to placebo, a long-acting beta agonist, an inhaled corticosteroid, or their combination.

Main Outcome(s) and Measure(s): All-cause mortality and composite cardiovascular events.

Results: Participants were 65±8 years, 75% were male, and 47% remained active smokers. Baseline BP and heart rate were 133±15/79±9 mmHg and 76±10 /min respectively. All-cause mortality increased in relation to high systolic (≥140 mmHg; hazard ratio (HR) 1.27 [95% CI 1.11-1.45]) or diastolic (>90 mmHg; HR 1.35 [95% CI 1.15-1.59]) BP and low systolic (<115 mmHg; HR 1.50 [95% CI 1.22-1.83]) or diastolic (<75 mmHg; HR 1.22 [95% CI 1.06-1.40]) BP. Higher heart rates (≥80 /min; HR 1.39 [95% CI 1.21-1.60]) and pulse pressures (≥60 mmHg;

HR 1.16 [95% CI 1.01-1.34]) were linearly-related to increases in all-cause mortality. The risks of cardiovascular events followed similar patterns to all-cause mortality. Similar findings were observed in subgroups of patients without established cardiovascular disease.

Conclusions and Relevance: Systolic and diastolic BP levels demonstrated a "U-shaped" relationship with all-cause mortality and cardiovascular events in patients with COPD and heightened cardiovascular risk. These findings extend the prognostic importance of BP to this growing group of patients and raise concerns that both high and low BP may pose health risks.

Trial Registration: ClinicalTrials.gov, number NCT01313676.

Introduction

High blood pressure (BP) is the leading risk factor for global deaths and disability.[1] Measurement of this simple, yet modifiable, biomarker has proven to be invaluable in the global battle against cardiovascular disease.[2] Mounting evidence further supports that an elevated heart rate is an additional easily-obtained hemodynamic metric independently predictive of all-cause as well as cardiovascular mortality.[3]

Patients with chronic obstructive pulmonary disease (COPD) die more frequently from cardiovascular than respiratory disease.[4-6] Over 6% of the United States' population has been told by a health professional that they have COPD,[7] and this prevalence appears to be similar in the 86 million patients with hypertension.[8] Thus, it is likely that over 5 million patients have co-morbid COPD and hypertension. This is important because a wealth of evidence accrued over the past half-century demonstrates that elevated BPs above ideal (<115/75 mm Hg) are monotonically (log-linearly) associated with increased cardiovascular events in the general population.[9,10] However, this relationship is more complex and perhaps non-linear among patients with established heart disease.[11-13] We therefore wanted to understand the prognostic value of BP specifically among individuals with COPD at heightened cardiovascular risk because this remains largely undescribed.

The Study to Understand Mortality and MorbidITy (SUMMIT) was a multi-center prospective, double-blind, randomized trial comparing placebo, a long-acting beta agonist (LABA), an inhaled corticosteroid (ICS), and their combination in patients with moderate COPD with or at risk for cardiovascular disease.[14,15] The primary (all-cause mortality) and secondary efficacy (composite cardiovascular events) outcomes did not differ between treatment arms.[16] Nevertheless, this large trial with well-adjudicated outcomes provides a unique opportunity to

explore in detail the nature of the relationships between BP and heart rate with all-cause mortality and cardiovascular events in a contemporary population of high-risk individuals with COPD.

Methods

SUMMIT included 16,485 participants enrolled across 1,368 centers in 46 counties with an average follow-up period for on-treatment cardiovascular outcomes of 1.7 years and on and post-treatment mortality of 1.9 years. The protocol, CONSORT diagram, and trial outcomes have been described in detail previously.[14,15] In brief, eligible participants included current or former smokers (≥10-pack-years) between the ages of 40 and 80 years, with a history of COPD and a post-bronchodilator FEV_1 ≥50 and ≤70% of the predicted value, a ratio of post-bronchodilator FEV_1 to forced vital capacity (FVC) ≤0.70, and a score ≥2 on the modified Medical Research Council dyspnea scale. Patients were required to be at increased cardiovascular risk (defined as being ≥60 years plus receiving medications for ≥2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral vascular disease) or have established disease (coronary artery disease, peripheral arterial disease, prior stroke or MI, or diabetes mellitus with target organ disease). The on-treatment composite secondary cardiovascular outcome included cardiovascular death, myocardial infarction (MI), stroke, unstable angina, and transient ischemic attack (TIA).

Hemodynamic Measurements

Study sites were instructed to perform vital signs prior to spirometry at all study visits and to measure systolic and diastolic BP as well as heart rate in the seated position after 5 min of rest. The BP and heart rate values obtained at the baseline visit (study visit #2) after the screening visit were used for these post-hoc analyses. The sphygmomanometer equipment and study staff that measured BP were consistent with the standard clinical practices of the investigators at each location.

Statistical Methods

The rates of all-cause mortality per 100 subject years were calculated as (100 x number of deaths)/total on- and post-treatment follow-up. The rates of on-treatment cardiovascular composite events were calculated as (100 x number of events)/total on-treatment follow-up. Both rates were calculated for 5 mmHg categories of systolic and diastolic BP and for each 5 beat/min category of heart rate. These results and the 95% confidence intervals (CIs)[17] were calculated across the range of baseline BP and heart rate values.

We calculated the hazard ratios (HR) and 95% CIs using Cox regression adjusted for the covariates of randomised treatment, age, sex, body-mass index (BMI), smoking habit and beta blocker use. The HRs were calculated for the time to death (or first cardiovascular endpoint) compared across 3 ranges of BP and heart rate values. These ranges for systolic (<115, ≥115 - <140, ≥140 mm Hg), diastolic BP (<75, ≥75 - <90, ≥90 mm Hg), and pulse pressure (<50, ≥50 - <60, ≥60 mm Hg) were selected based upon their clinical relevance and reasonable distribution

within the population values. Similar models were calculated for heart rate ranges (<70, ≥70 - <80, ≥ 80 beats per minute).

Results

Demographic and Hemodynamic Characteristics

The average age of study participants was 65±8 years, 75% were male, and 47% remained active smokers. The mean body-mass index was 28±6 kg/m^2. Most individuals were white (81%), while 17% and 2% were Asian or another race, respectively. By our study definition, 71% of participants had cardiovascular disease. Excluding diabetes plus target organ disease from this definition, 66% of patients had "overt" disease (e.g., prior MI). As previously reported,[16] the population of patients were well-treated with contemporary medications with more than half on statins (64-66%) and anti-platelet (51-53%) therapies.

While there was a large overall range, the average baseline BP among participants was within the controlled category (<140/90 mm Hg; **Table 1**). Given the age and co-morbidities of the participants, nearly 90% were receiving some type of antihypertensive medication with the most common being a renin-angiotensin system inhibitor or antagonist (**Table 2**).

Baseline Hemodynamic Parameters, All-Cause Mortality and Cardiovascular Risk

Table 3 shows the risks for all-cause mortality and cardiovascular composite events in association with BP and heart rate levels measured at baseline among SUMMIT participants. Compared with the middle range, the risks of an event were higher in those with systolic and diastolic BP levels in either the higher or lower ranges (**Figures S1, S2, S3 and S4; online supplement**). The HRs for mortality for systolic BP were: high range vs middle range HR=1.27,

low range vs middle range HR=1.50. The HRs for mortality for diastolic BP were: high range vs middle range HR=1.35, low range vs middle range HR=1.22 (**Table 3**). Conversely, there appeared to be an increasing risk of death with increasing heart rate only (**Figure S5**) (high range vs middle range HR=1.39, low range vs middle range HR=0.83, **Table 3**), with a similar trend for cardiovascular events (**Figure S6**). Like heart rate, only high (but not low) pulse pressure was associated with increased risk of an event (**Figures S7 and S8**) (for mortality, high range vs middle range HR=1.17, **Table 3**).

Relationships between BP and heart rate with Morbidity and Cardiovascular Events

The associations between all-cause mortality and systolic and diastolic BP across the entire range of baseline study values were consistent with a generally "U"-shaped relationship: progressively higher and lower values outside optimal ranges being associated with increasing mortality rates (**Figures 1A and 1B**). The nadir of risk visually appears to be among patients with a BP from 125-135/75-90 mm Hg. There appears to be more of a linear relationship between heart rate and mortality (particularly disregarding the extreme outliers with heart rates <45 beats/minute, (**Figure 2A**). However, there appears to be a less clear relationship between pulse pressure and mortality (**Figure 2B**). When similarly plotted, the risks associated with cardiovascular events followed a similar pattern (**Figures S9-S12**). In models including additional covariates (e.g., other anti-hypertensive medications), there were no consistent significant changes in the outcomes.

Baseline Hemodynamic Characteristics, All-Cause Mortality and Cardiovascular Risk by Patient History

We investigated the effects of hemodynamic parameters on the risk of events in the subgroups of patients with and without previous coronary heart disease and in the subgroups of patients with a history of cardiovascular disease (per trial definition) and those only at heightened cardiovascular risk (i.e., no overt disease) (**Tables S1 and S2**). In general, the patterns of outcomes were similar in each group to the main findings. The higher risks of mortality and cardiovascular events due to low systolic and diastolic BP were also observed in patients at heightened risk but without overt disease. This supports that this "U-shaped" relationship was not confined only to this with a prior cardiovacular event or underlying disease.

Discussion

Elevated BP levels above ideal (>115/75 mm Hg) are monotonically linked to increased morbidity and mortality in the general population.[9,10] However, the prognostic value of high BP specifically among individuals with COPD remains poorly described. Here, we report for the first time that both high and low BPs are associated with increased all-cause mortality and cardiovascular events in patients with COPD at high risk for cardiovascular events or with cardiovascular disease. This relationship was observed even among patients without a history of a prior cardiovascular event or established disease. In contrast, only a higher heart rate and pulse pressure were associated with increases in risks. These findings raise warnings that health care providers may need to be concerned about a worse prognosis in patients with COPD both with high as well as low systolic and diastolic BPs.

Outside the context of COPD, the relationship between hemodynamic measures and mortality has been determined in extremely large datasets, yielding high confidence in the

results. In an analysis of over 1 million people without vascular disease at the initiation of longitudinal study, BP was associated with outcomes in a monotonic log-linear fashion.[9] A more recent analysis confirmed these findings in 1.25 million people initially free of cardiovascular disease.[10] Conversely, in patients with coronary heart disease, a "U-shaped" relationship has been variably observed, as exemplified by a recent global observational study of over 22,000 patients.[11] Similarly, systolic and diastolic BP were recently found to have U-shaped relationships with all-cause mortality among participants at high risk for cardiovascular events in the TRANSCEND and ONTARGET trials.[18] Yet, earlier studies have not consistently confirmed these findings, particularly after adjusting for confounding factors.[12] The topic of a "U-shaped" or "J-curve" relationship between BP and cardiovascular outcomes in patients with coronary heart disease has generated significant controversy over the years.[12,13] The main concerns pertain to the clinical implications. Are low BPs a marker of poor underlying health (i.e., "reverse-causation") or do treatment-induced reductions below a threshold (particularly of diastolic BP) lead to decreased coronary perfusion? Are additional vascular territories such as cerebral perfusion also impacted? Do these risks only pertain to patients with pre-existing coronary atherosclerosis? What is the optimal BP level to target with antihypertensive treatment in order to reduced cardiovascular risk? Despite decades of research varying opinions persist[12,13]. The debate has intensified recently following the SPRINT study[19] and a network meta-analysis (both suggesting that an optimal systolic BP level is 120-125 mm Hg).[20] Our observational findings cannot specifically address these issues. However, they do raise concerns that these questions may also apply to high-risk patients with COPD.

Despite availability of robust data on relationships between hemodynamic measures and mortality, there are scant data in the population of patients with COPD. Consistent with our

findings and those in other populations,[3] resting heart rate has been reported in the past to predict mortality in COPD[21] and cardiovascular mortality in coronary artery disease.[22] A fast heart rate may be a risk marker of autonomic imbalance heightening the potential for arrhythmias or sudden death, and it may directly promote myocardial ischemia or damage. Moreover, faster heart rates might be an indicator of poor fitness or severity of illness. It is important to note, however, that there remains no trial evidence that pharmacologically lowering heart rate (e.g. beta blockade) directly translates into a reduction in risk in patients with COPD. In a clinical setting in which higher heart rate is associated with worse outcomes, ivabradine lowered heart rate in a trial of patients with stable coronary artery disease and left ventricular systolic dysfunction, but did not improve mortality.[23] Regardless, we confirm here in high-risk patients with COPD that increases in heart rates are associated not only with mortality, but also excess cardiovascular events.

Patients 45 years of age and older, and meeting the Global Initiative for Obstructive Lung Disease (GOLD) criteria for COPD in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS) were studied by Mannino et al.[24] They found an increased risk of hospitalization and mortality in patients with COPD and hypertension—considered as a dichotomous variable—compared to patients with impaired lung function. Our study is more comprehensive in several respects, including our assessment of hemodynamic variables as continuous measures, evaluating the impact of both high and low levels, and our specific analyses of systolic BP, diastolic BP, pulse pressure, and heart rate. Perhaps owing to concern for the effect of specific drug classes (e.g., beta blockers), some prior work has been done describing the relationships between specific antihypertensive drugs and cardiovascular outcomes in COPD. Indeed, a recent meta-analysis supports the safety and overall cardiovascular

protection of beta blockade in patients with COPD.[25] We similarly observed no evidence of harm related to beta blocker usage in the SUMMIT trial (manuscript in review). Herrin and colleagues reported in a retrospective analysis that two-drug antihypertensive combinations including a thiazide diuretic were more effective for preventing heart failure hospitalizations in patients with COPD.[26] The paucity of overall evidence and lack of prospective outcome trials means that the optimal BP target and ideal antihypertensive regimen for patients with COPD must remain a matter of expert opinion.

There are several limitations to note. Foremost, this was a post-hoc observational study and the findings must therefore be considered hypothesis-generating. The methodology for measurement of BP in the SUMMIT trial was not governed by strict protocols and multiple aspects pertaining to its accuracy likely varied across the 1,368 sites. We only evaluated the outcomes based upon BP levels at the start of the trial and not time-averaged values. These facts would tend to bias observational analyses toward the null. Nonetheless, significant health associations with a single BP reading were still detected. More rigorous standardization as well as multiple determinations of BP (or ambulatory BP monitoring) would likely have yielded an even more robust signal. We believe our findings therefore highlight the strength of the linkage between BP with health risks in patients with COPD. Our findings do not directly impugn low BP as being harmful *per se*. We cannot exclude that it may simply be a marker of poor health or "reverse-causation." Regardless, our study represents the first large-scale evaluation of the nature of the relationship between BP and all-cause mortality and cardiovascular events (which were well-adjudicated in a clinical trial setting) specifically in a population of patients with COPD.

Conclusions

Both high and low BPs are associated with increased mortality and excess cardiovascular events, whereas faster heart rates are linked to health risks, in individuals with COPD at heightened cardiovascular risk. Further studies are warranted to confirm our findings and investigate the clinical implications as well as the benefits, optimal anti-hypertensive strategies, and BP treatment goals in this important and growing global population of patients.

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Table 1. Participant Hemodynamic Measures.

	n	Mean (SD)	Minimum	Maximum
Systolic BP (mm Hg)	16482	133 (15)	70	220
Diastolic BP (mm Hg)	16482	79 (9)	40	140
Pulse Pressure (mm Hg)	16482	54 (12)	13	120
Heart Rate (beats/min)	16481	76 (10)	40	147

Table 2. Anti-Hypertensive Medications at Study Entry.

	Number of participants	Percentage
Number of Medications		
None	1,740	11%
1	5,761	35%
2	4,777	29%
≥3	4,207	26%
Medication Class		
Beta blockers	5,159	31%
Calcium channel blockers	5,690	35%
Diuretics	5,449	33%
ACEi* or ARB†	10,981	67%
Other	763	5%

*ACEi, angiotensin-converting enzyme inhibitor; †ARB, angiotensin receptor blocker

Table 3. Study Events by Baseline Blood Pressures and Heart Rates.

	All-Cause Mortality		CVD Event	
	Hazard ratio	**95% CI**	**Hazard ratio**	**95% CI**
Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=9,144)				
<115 mm Hg (n=1,394)	1.50	1.22-1.83	1.30	1.00-1.69
≥140 mm Hg (n=5,944)	1.27	1.11-1.45	1.19	1.01-1.39
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=8,875)				
<75 mm Hg (n=4,565)	1.22	1.06-1.40	1.37	1.15-1.63
≥90 mm Hg (n=3,042)	1.35	1.15-1.95	1.53	1.26-1.85
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=5,899)				
<50 mm Hg (n=4,993)	1.03	0.88-1.21	1.09	0.90-1.32
≥60 mm Hg (n=5,590)	1.16	1.01-1.34	1.21	1.01-1.45
Heart Rate (HR vs. ≥70 to <80 beats/min; n=6,658)				

	< 70 beats/min (n=3,896)	0.83	0.70-0.99	0.93	0.76-1.13
	≥80 beats/min (n=5,927)	1.39	1.21-1.60	1.22	1.02-1.44

CI, confidence interval; CVD, cardiovascular disease (secondary composite outcome).

*The hazard ratio represents the risks compared to the middle ranges of values for each parameter

Figure Legends.

Figure 1A. All-cause Mortality and Systolic Blood Pressure

Rate of death per 100 subject years is shown, grouped in 5 mmHg categories according to baseline systolic blood pressure.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure 1B. All-cause Mortality and Diastolic Blood Pressure

Rate of death per 100 subject years is shown, grouped in 5 mmHg categories according to baseline diastolic blood pressure.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure 2A. All-cause Mortality and Heart Rate

Rate of death per 100 subject years is shown, grouped in 5 beats/minute categories according to baseline heart rate.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure 2B. All-cause Mortality and Pulse Pressure

Rate of death per 100 subject years is shown, grouped in 5 mmHg categories according to baseline pulse pressure.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure 1.

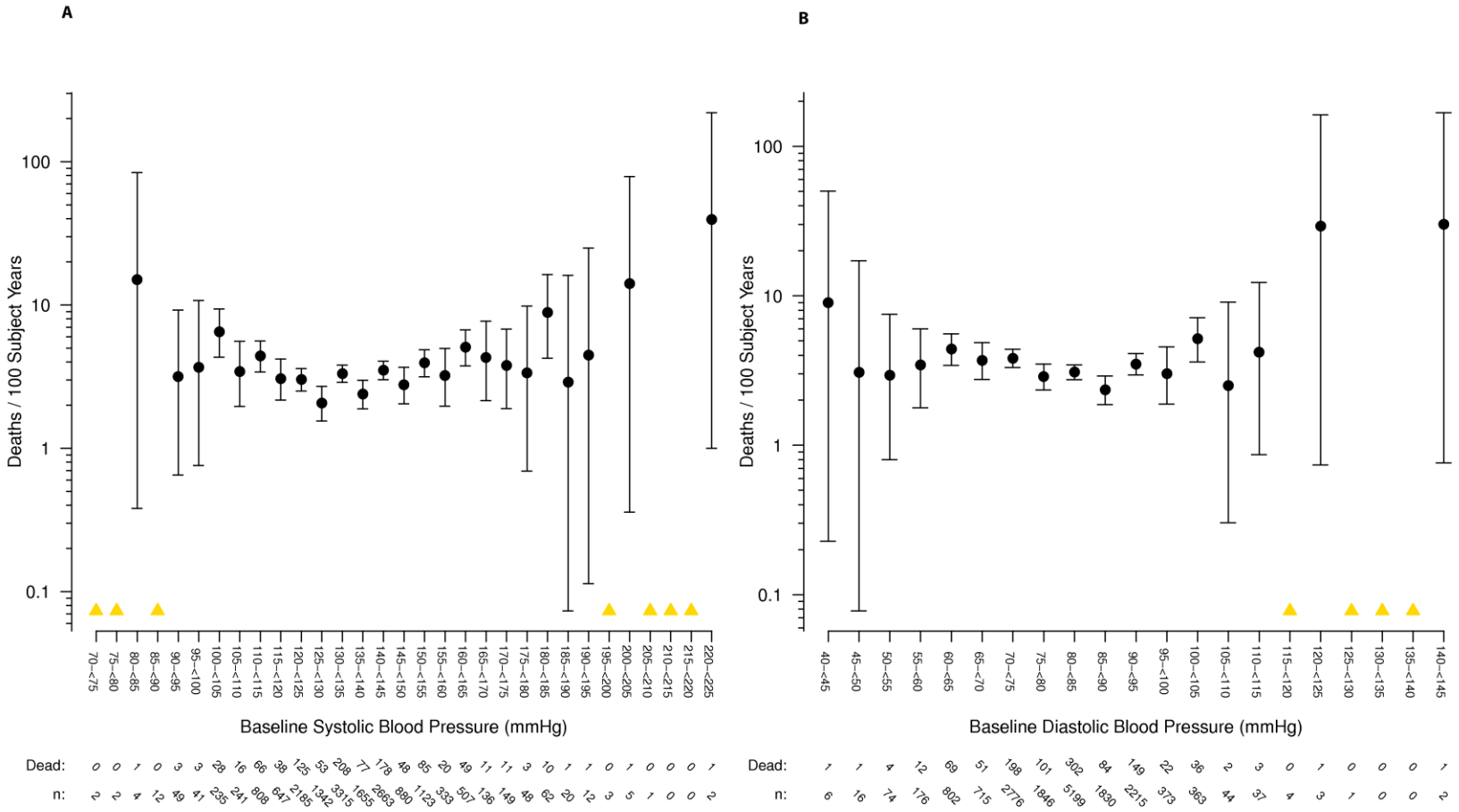
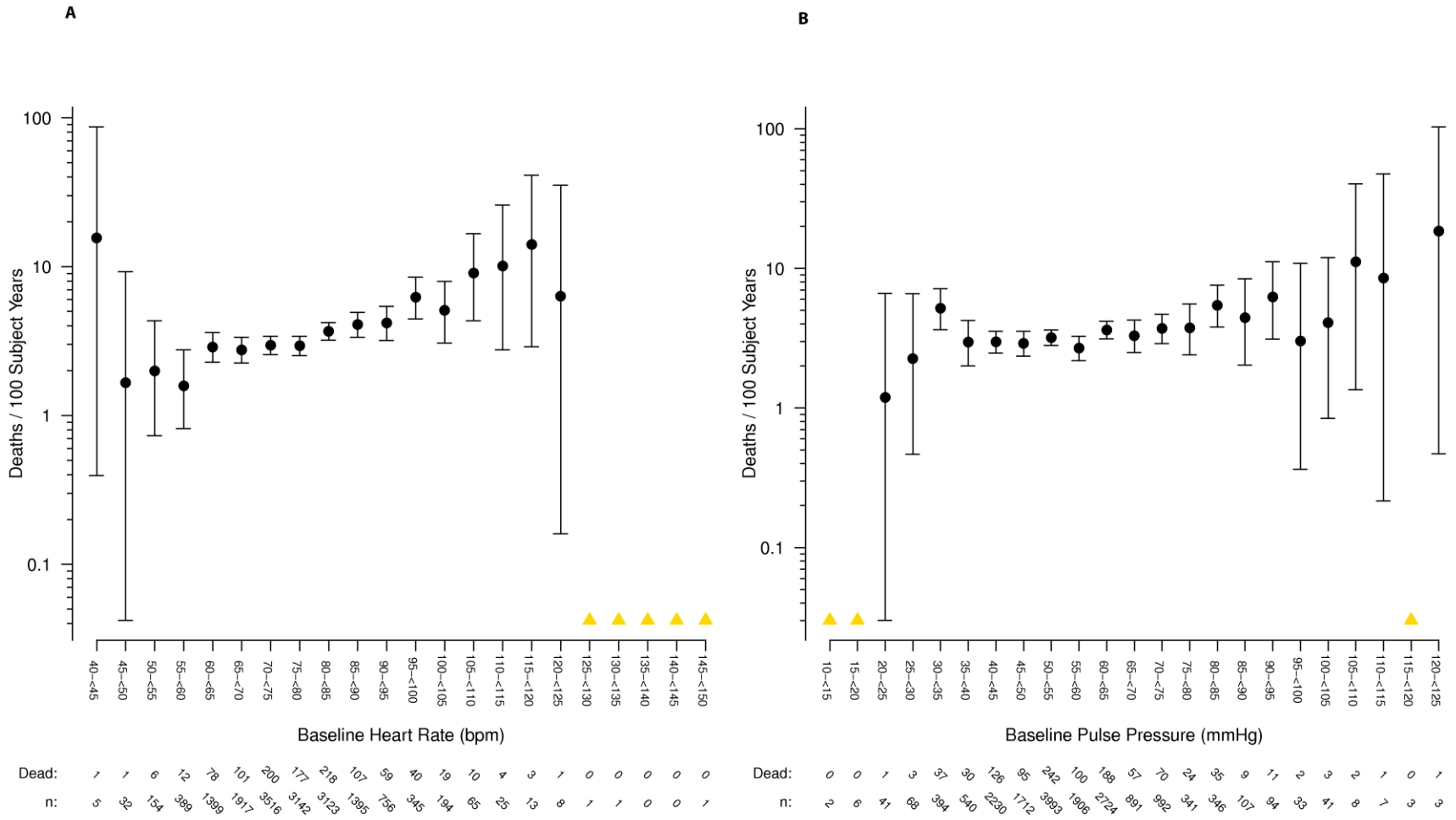

A
Deaths / 100 Subject Years
100
10
1
0.1
70–<75 75–<80 80–<85 85–<90 90–<95 95–<100 100–<105 105–<110 110–<115 115–<120 120–<125 125–<130 130–<135 135–<140 140–<145 145–<150 150–<155 155–<160 160–<165 165–<170 170–<175 175–<180 180–<185 185–<190 190–<195 195–<200 200–<205 205–<210 210–<215 215–<220 220–<225
Baseline Systolic Blood Pressure (mmHg)
Dead: 0 0 1 0 3 3 28 16 68 38 125 53 208 77 178 48 85 20 49 11 11 3 10 1 1 0 1 0 0 0 0 1
n: 2 2 4 12 49 41 235 241 808 647 2185 1342 3315 1655 2663 880 1123 333 507 136 149 48 62 20 12 3 5 1 0 0 0 2
B
Deaths / 100 Subject Years
100
10
1
0.1
40–<45 45–<50 50–<55 55–<60 60–<65 65–<70 70–<75 75–<80 80–<85 85–<90 90–<95 95–<100 100–<105 105–<110 110–<115 115–<120 120–<125 125–<130 130–<135 135–<140 140–<145
Baseline Diastolic Blood Pressure (mmHg)
Dead: 1 1 4 12 69 51 198 101 302 84 149 22 36 2 3 0 1 0 0 0 1
n: 6 16 74 176 802 715 2776 1846 5199 1830 2215 373 363 44 37 4 3 1 0 0 2

Figure 2.


A
Deaths / 100 Subject Years
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0.1
40–<45
45–<50
50–<55
55–<60
60–<65
65–<70
70–<75
75–<80
80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
125–<130
130–<135
135–<140
140–<145
145–<150
Baseline Heart Rate (bpm)
Dead: 1 1 6 12 78 101 200 177 218 107 59 40 19 10 4 3 1 0 0 0 0 0
n: 5 32 154 389 1399 1917 3516 3142 3123 1395 756 345 194 65 25 13 8 1 1 0 0 1
B
Deaths / 100 Subject Years
100
10
1
0.1
10–<15
15–<20
20–<25
25–<30
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80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
Baseline Pulse Pressure (mmHg)
Dead: 0 0 1 3 37 30 126 95 242 100 188 57 70 24 35 9 11 2 3 2 1 0 1
n: 2 6 41 68 394 540 2230 1712 3993 1906 2724 891 992 341 346 107 94 33 41 8 7 3 3

Supplemental Data

Table S1. Study Events by Baseline Blood Pressures and Heart Rates – Split by Cardiovascular History and Risk at Screening					
			All-Cause Mortality		CVD Event	
			HR*	95% CI	HR	95% CI
Age 40-60 with CV Disease						
Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=2,028)						
	≥140 mm Hg (n=1,190)		1.30	0.92-1.86	1.38	0.94-2.04
	<115 mm Hg (n=317)		1.26	0.72-2.20	1.12	0.55-2.28
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=1,962)						
	≥90 mm Hg (n=853)		1.34	0.91-1.97	1.67	1.09-2.54
	<75 mm Hg (n=720)		1.08	0.70-1.66	1.26	0.77-2.06
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=1,310)						
	≥60 mm Hg (n=901)		1.34	0.90-2.00	1.10	0.70-1.72
	<50 mm Hg (n=1,324)		0.87	0.58-1.30	0.84	0.54-1.31
Heart Rate (HR vs. ≥70 to <80 beats/min; n=1,514)						
	≥80 beats/min (n=1,294)		1.63	1.13-2.35	1.22	0.82-1.81
	< 70 beats/min (n=726)		0.95	0.57-1.58	0.58	0.32-1.05
Age 60-80 with CV Disease						

Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=4,431)					
	≥140 mm Hg (n=2,962)	1.27	1.08-1.50	1.13	0.93-1.37
	<115 mm Hg (n=732)	1.44	1.12-1.85	1.29	0.95-1.76
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=4,279)					
	≥90 mm Hg (n=1,339)	1.41	1.14-1.73	1.46	1.15-1.86
	<75 mm Hg (n=2,507)	1.18	0.99-1.40	1.32	1.07-1.62
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=2,866)					
	≥60 mm Hg (n=2,959)	1.04	0.87-1.25	1.22	0.98-1.51
	<50 mm Hg (n=2,300)	1.01	0.83-1.23	1.07	0.84-1.35
Heart Rate (HR vs. ≥70 to <80 beats/min; n=3,215)					
	≥80 beats/min (n=2,741)	1.36	1.14=1.62	1.29	1.05-1.60
	< 70 beats/min (n=2,169)	0.78	0.63-0.97	0.96	0.75-1.21
Age 60-80 with CV Risk but not Disease					
Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=2,600)					
	≥140 mm Hg (n=1,710)	1.23	0.94-1.62	1.15	0.77-1.71
	<115 mm Hg (n=330)	1.69	1.10-2.59	1.21	0.57-2.54
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=2,539)					

	≥90 mm Hg (n=803)	1.20	0.85-1.71	1.52	0.92-2.51
	<75 mm Hg (n=1,298)	1.31	0.98-1.74	1.50	0.97-2.32
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=1,662)					
	≥60 mm Hg (n=1,661)	1.49	1.09-2.02	1.36	0.85-2.17
	<50 mm Hg (n=1,317)	1.27	0.91-1.78	1.60	0.98-2.61
Heart Rate (HR vs. ≥70 to <80 beats/min; n=1,859)					
	≥80 beats/min (n=1,815)	1.37	1.03-1.82	1.02	0.67-1.55
	< 70 beats/min (n=966)	0.81	0.55-1.20	0.88	0.52-1.50

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease (secondary composite outcome).

*The HR represents the risks compared to the middle ranges of values for each parameter

183 patients did not meet the CV risk/disease inclusion criteria, so are not included in this table.

Table S2. Study Events by Baseline Blood Pressures and Heart Rates – Split by Previous MI/CABG/PCI					
			All-Cause Mortality		CVD Event	
			HR*	95% CI	HR	95% CI
Previous MI/CABG/PCI						
Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=1,908)						
	≥140 mm Hg (n=1,090)		1.29	0.99-1.68	1.31	1.00-1.74
	<115 mm Hg (n=436)		1.09	0.74-1.60	1.07	0.71-1.62
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=1,721)						
	≥90 mm Hg (n=490)		1.15	0.80-1.65	1.37	0.95-1.99
	<75 mm Hg (n=1,224)		0.94	0.72-1.23	1.29	0.97-1.71
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=1,140)						
	≥60 mm Hg (n=1,174)		0.95	0.72-1.27	1.20	0.89-1.63
	<50 mm Hg (n=1,121)		0.86	0.63-1.17	0.81	0.58-1.14
Heart Rate (HR vs. ≥70 to <80 beats/min; n=1,346)						
	≥80 beats/min (n=949)		1.51	1.13-2.01	0.96	0.70-1.31
	< 70 beats/min (n=1,139)		0.91	0.67-1.24	0.70	0.51-0.96
No Previous MI/CABG/PCI						
Systolic blood pressure (HR vs. ≥115 to <140 mm Hg; n=7,235)						

	≥140 mm Hg (n=4,854)	1.28	1.10-1.48	1.17	0.96-1.42
	<115 mm Hg (n=958)	1.68	1.33-2.13	1.36	0.97-1.91
Diastolic blood pressure (HR vs. ≥75 to <90 mm Hg; n=7,154)					
	≥90 mm Hg (n=2,552)	1.42	1.19-1.71	1.63	1.30-2.05
	<75 mm Hg (n=3,341)	1.32	1.12-1.55	1.32	1.05-1.64
Pulse Pressure (HR vs. ≥50 to <60 mm Hg; n=4,759)					
	≥60 mm Hg (n=4,416)	1.25	1.05-1.47	1.21	0.97-1.51
	<50 mm Hg (n=3,872)	1.09	0.91-1.31	1.21	0.96-1.53
Heart Rate (HR vs. ≥70 to <80 beats/min; n=5,312)					
	≥80 beats/min (n=4,978)	1.37	1.18-1.60	1.41	1.15-1.74
	< 70 beats/min (n=2,757)	0.78	0.63-0.97	1.04	0.80-1.35

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease (secondary composite outcome).

*The HR represents the risks compared to the middle ranges of values for each parameter

Supplementary Figure Legends.

Figure S1. All-cause Mortality and Systolic Blood Pressure Ranges

Kaplan Meier plot of time to death by systolic blood pressure ranges.

Figure S2. All-cause Mortality and Diastolic Blood Pressure Ranges

Kaplan Meier plot of time to death by diastolic blood pressure ranges.

Figure S3. Cardiovascular Composite Events and Systolic Blood Pressure Ranges

Kaplan Meier plot of time to death by systolic blood pressure ranges.

Figure S4. Cardiovascular Composite Events and Diastolic Blood Pressure Ranges

Kaplan Meier plot of time to death by diastolic blood pressure ranges.

Figure S5. All-cause Mortality and Heart Rate Ranges

Kaplan Meier plot of time to death by heart rate ranges.

Figure S6. Cardiovascular Composite Events and Heart Rate Ranges

Kaplan Meier plot of time to death by heart rate ranges.

Figure S7. All-cause Mortality and Pulse Pressure Ranges

Kaplan Meier plot of time to death by pulse pressure ranges.

Figure S8. Cardiovascular Composite Events and Pulse Pressure Ranges

Kaplan Meier plot of time to death by pulse pressure ranges.

Figure S9. Cardiovascular Composite Events and Systolic Blood Pressure

Rate of CV events per 100 subject years is shown, grouped in 5 mm Hg categories according to baseline systolic blood pressure.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure S10. Cardiovascular Composite Events and Diastolic Blood Pressure

Rate of CV events per 100 subject years is shown, grouped in 5 mm Hg categories according to baseline diastolic blood pressure.

Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure S11. Cardiovascular Composite Events and Pulse Pressure

Rate of CV events per 100 subject years is shown, grouped in 5 mm Hg categories according to baseline pulse pressure.

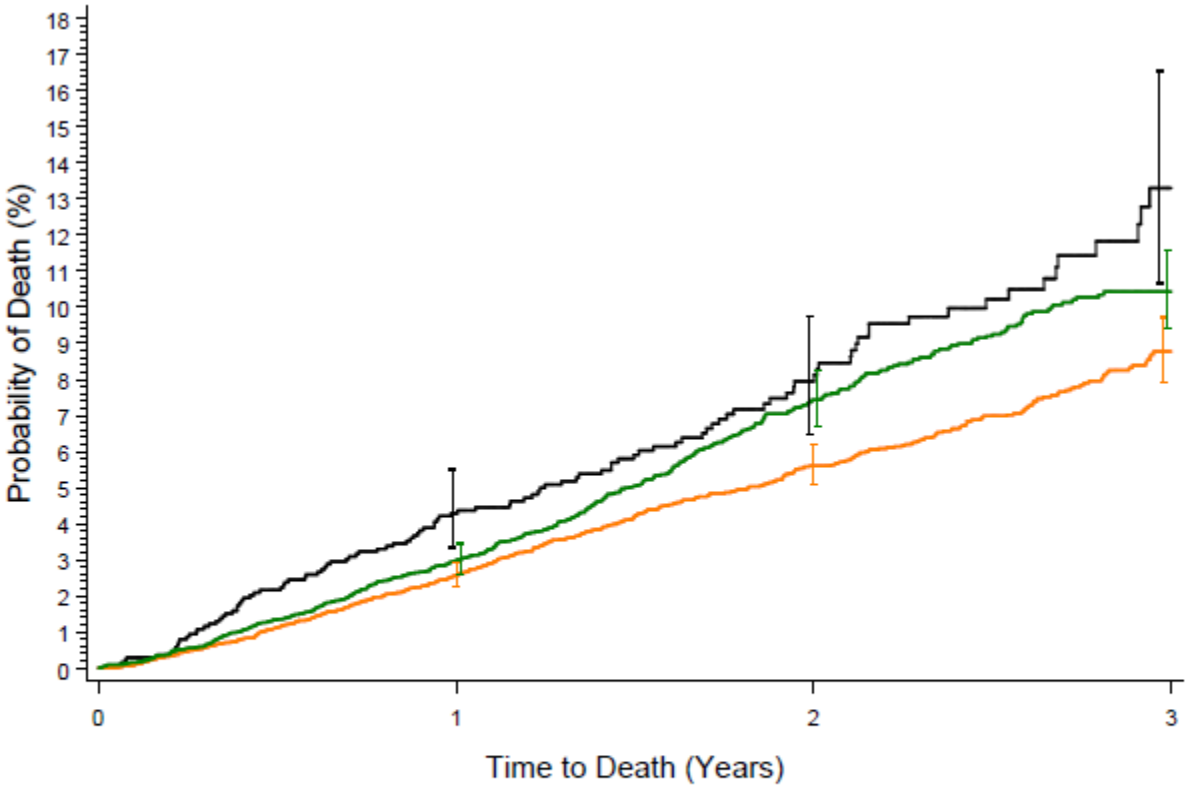
Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure S12. Cardiovascular Composite Events and Heart Rate

Rate of CV events per 100 subject years is shown, grouped in 5 beats/minute categories according to baseline heart rate.

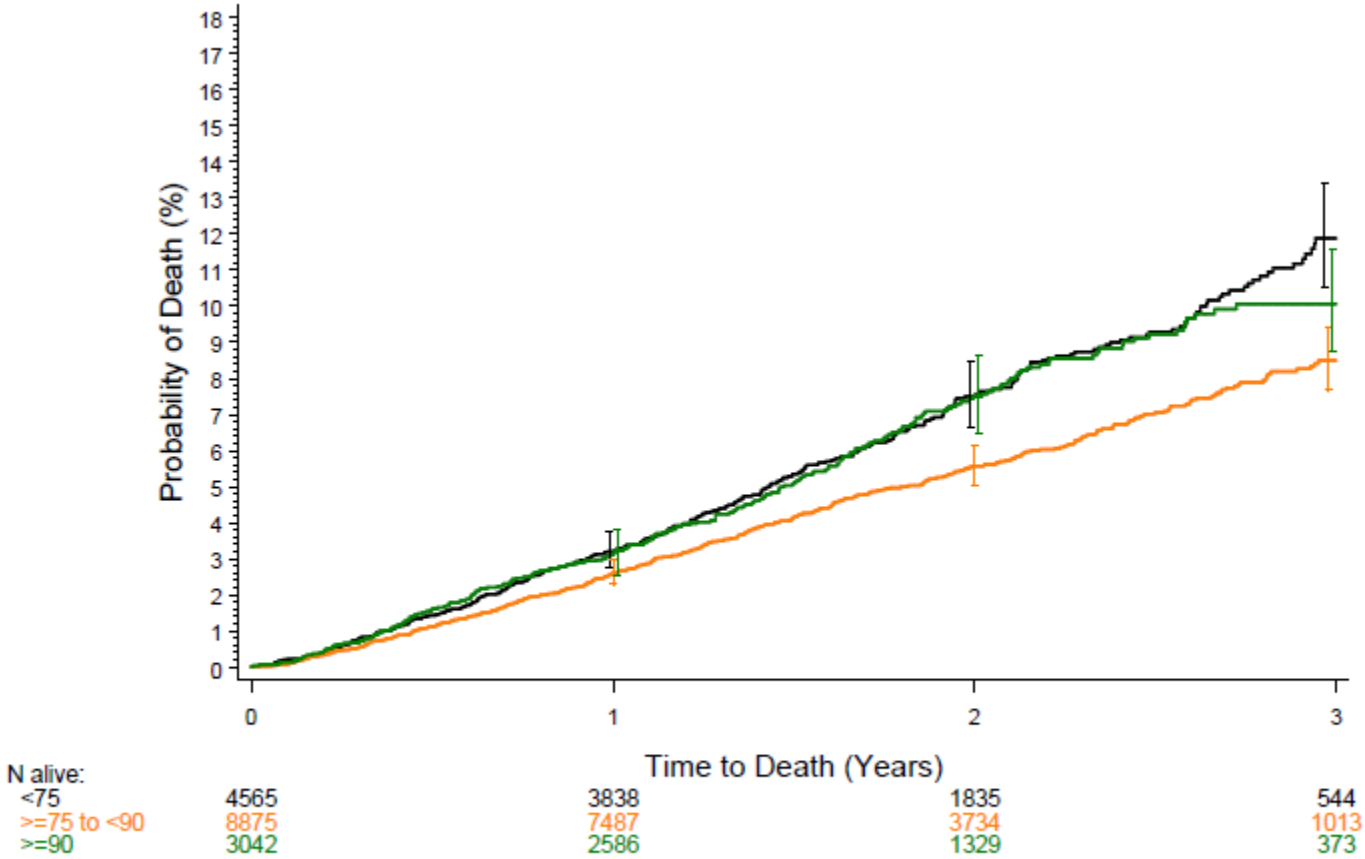
Note: A yellow triangle represents categories where there were zero deaths, so a rate could not be calculated.

Figure S1



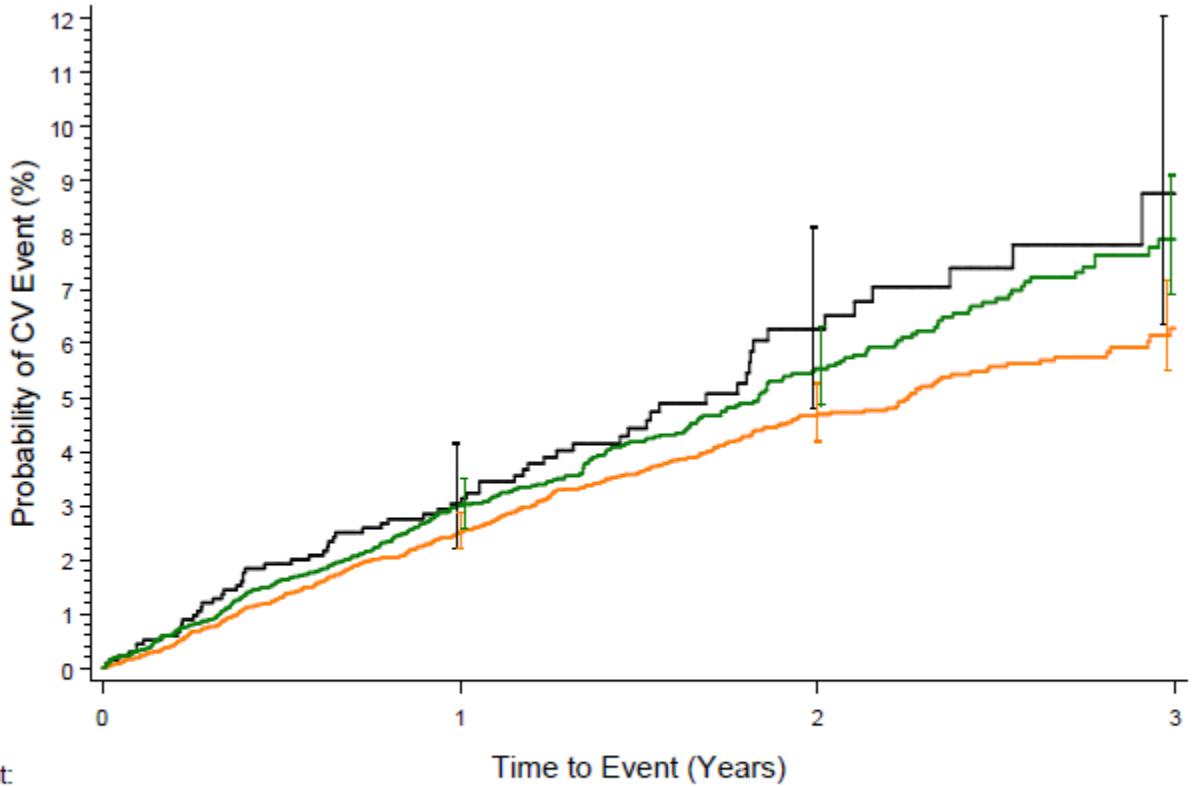
Note: Primary endpoint includes deaths occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N alive' denotes the number of subjects who are alive and are continuing follow-up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

Figure S2



Note: Primary endpoint includes deaths occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N alive' denotes the number of subjects who are alive and are continuing follow-up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

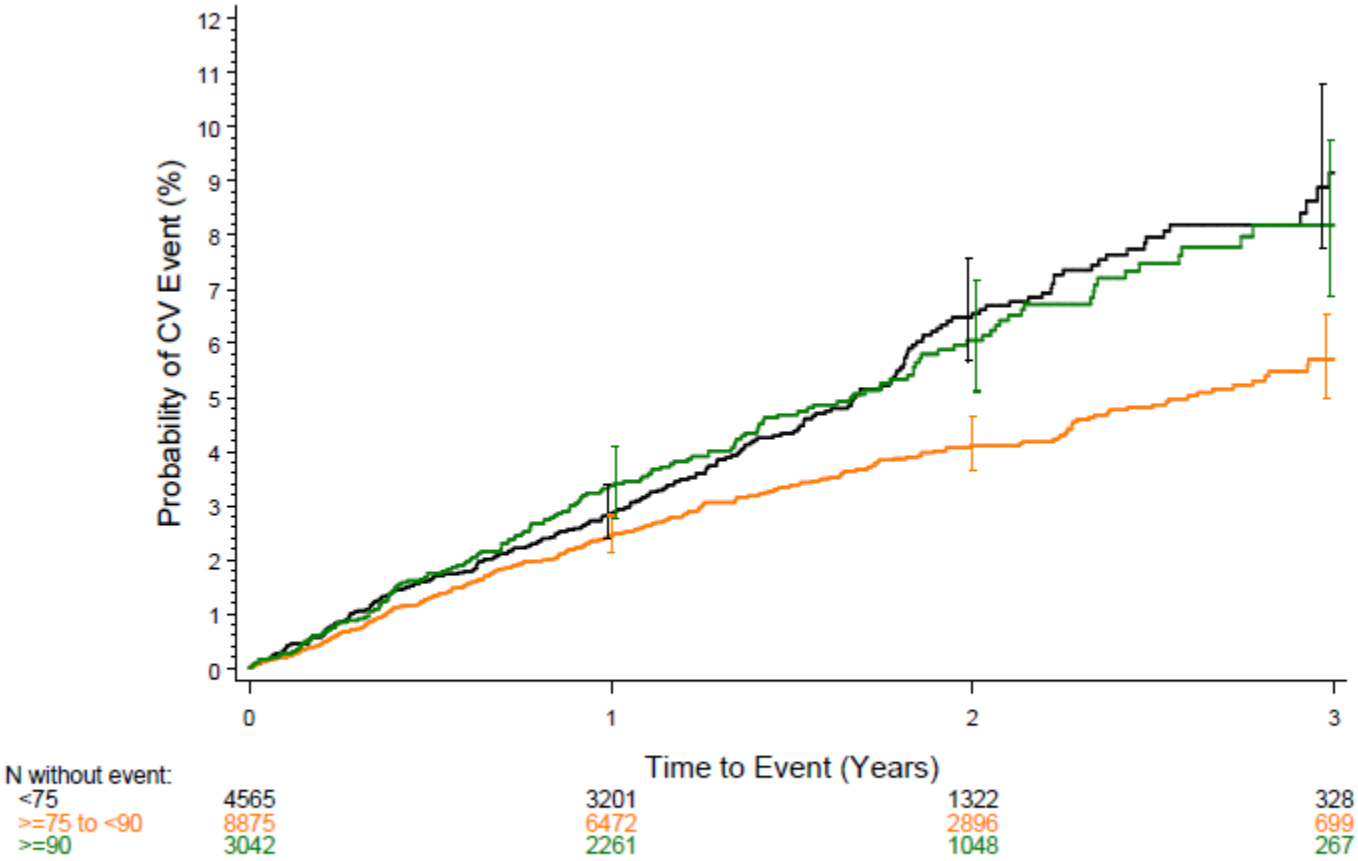
Figure S3



N without event:				
<115	1394	971	383	73
>=115 to <140	9144	6666	2905	688
>=140	5944	4297	1978	533

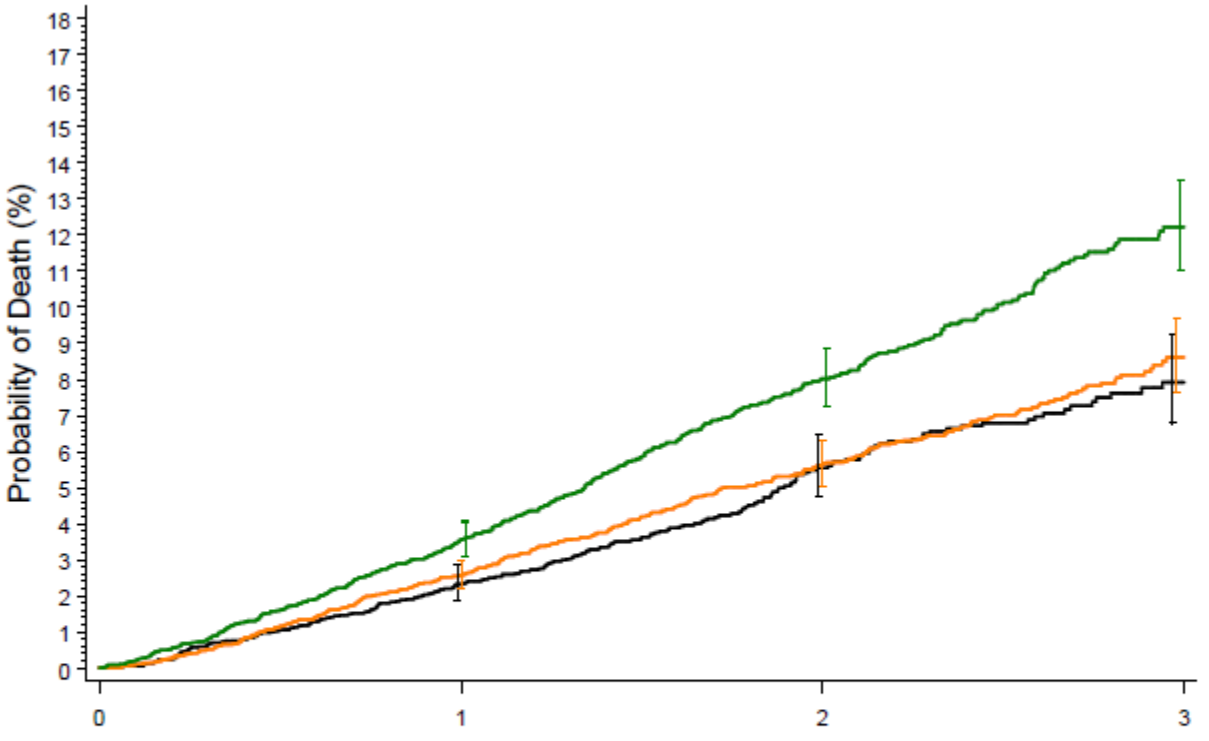
Note: Secondary endpoint includes on−treatment cardiovascular composite events occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N without event' denotes the number of subjects who have not had an event and are continuing follow−up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

Figure S4



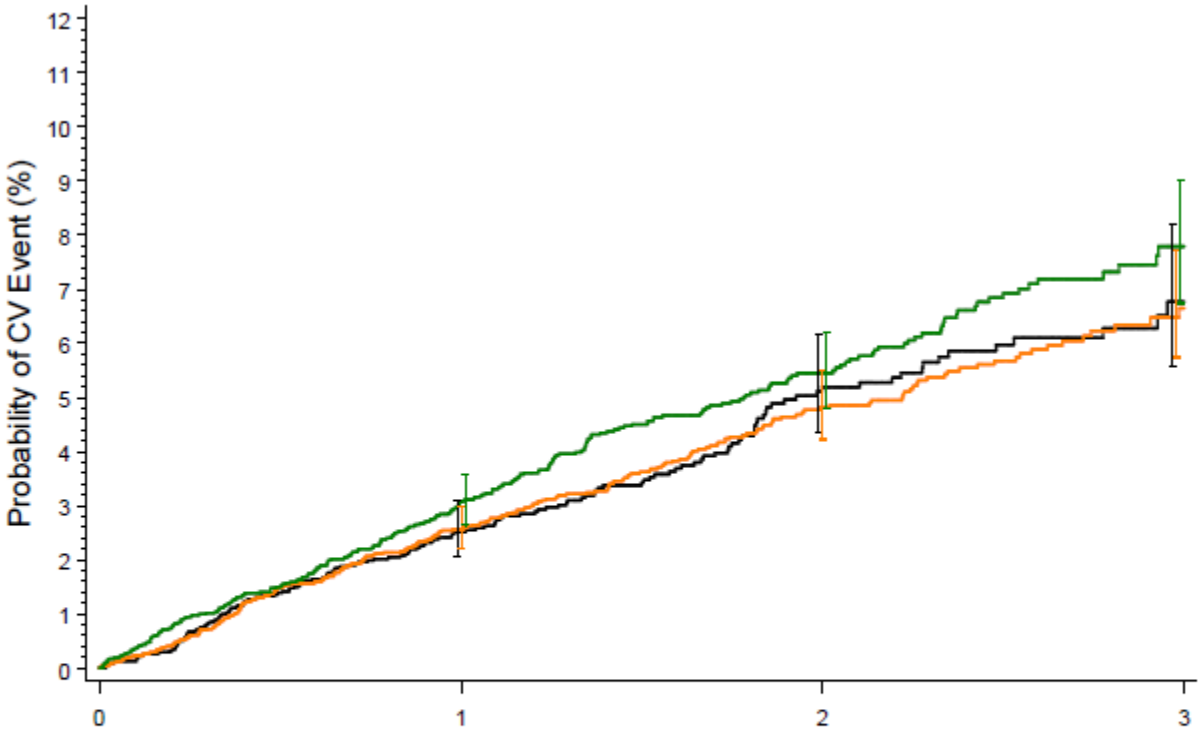
Note: Secondary endpoint includes on-treatment cardiovascular composite events occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N without event' denotes the number of subjects who have not had an event and are continuing follow-up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

Figure S5



Note: Primary endpoint includes deaths occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N alive' denotes the number of subjects who are alive and are continuing follow−up immediately after the time point.
Note: Heart Rate units are beats per minute (beats/min).

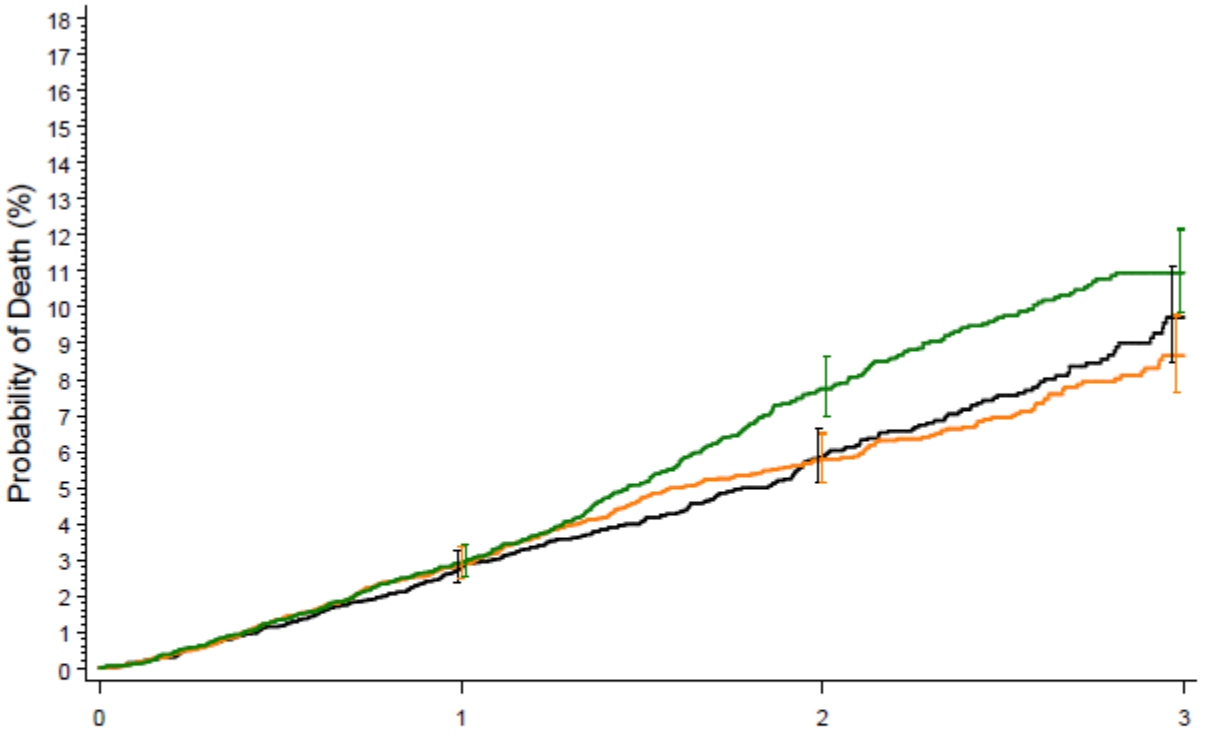
Figure S6



N without event:				
<70	3896	2815	1196	336
>=70 to <80	6658	4899	2195	523
>=80	5927	4219	1875	435

Note: Secondary endpoint includes on−treatment cardiovascular composite events occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N without event' denotes the number of subjects who have not had an event and are continuing follow−up immediately after the time point.
Note: Heart Rate units are beats per minute (beats/min).

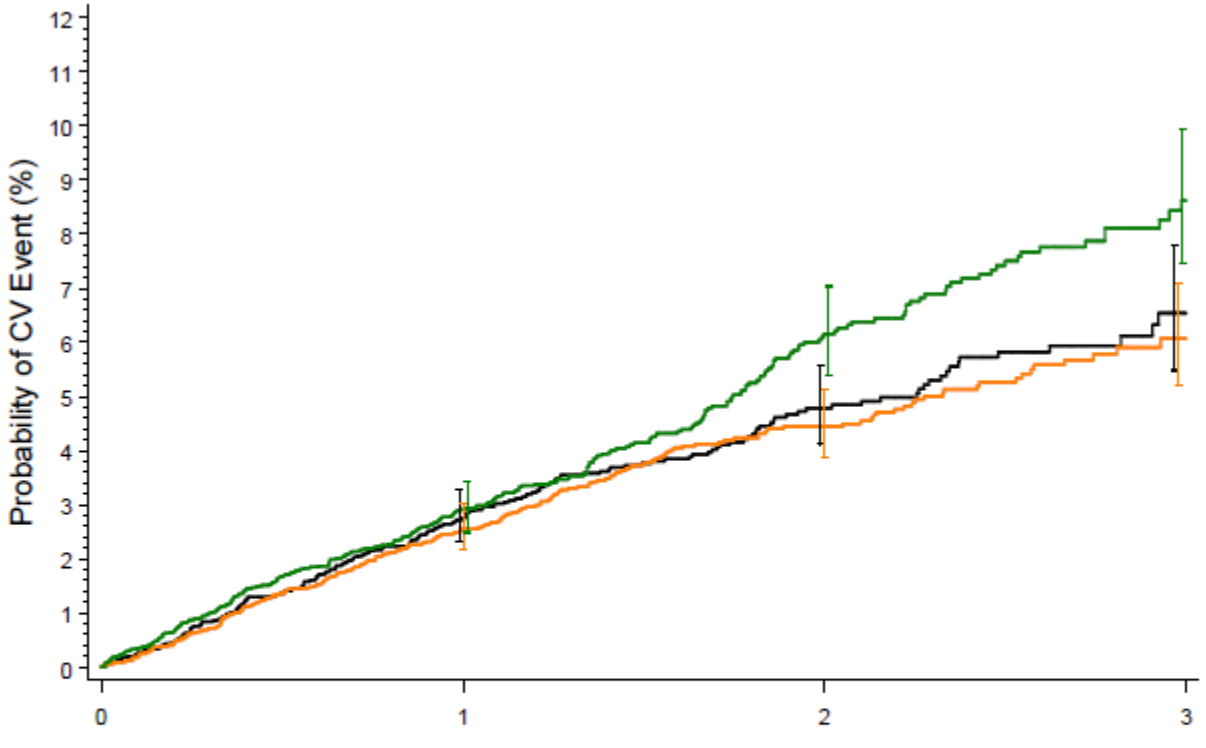
Figure S7



N alive:				
<50	4993	4226	2056	545
>=50 to <60	5899	4977	2518	684
>=60	5590	4708	2324	701

Note: Primary endpoint includes deaths occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N alive' denotes the number of subjects who are alive and are continuing follow-up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

Figure S8



N without event:				
<50	4993	3624	1537	348
>=50 to <60	5899	4331	1963	467
>=60	5590	3979	1766	479

Note: Secondary endpoint includes on−treatment cardiovascular composite events occurring on or before Common End Date.
Note: 95% Confidence Intervals provided at yearly intervals.
Note: 'N without event' denotes the number of subjects who have not had an event and are continuing follow−up immediately after the time point.
Note: Blood pressure units are millimeters of mercury (mmHg).

Figure S9

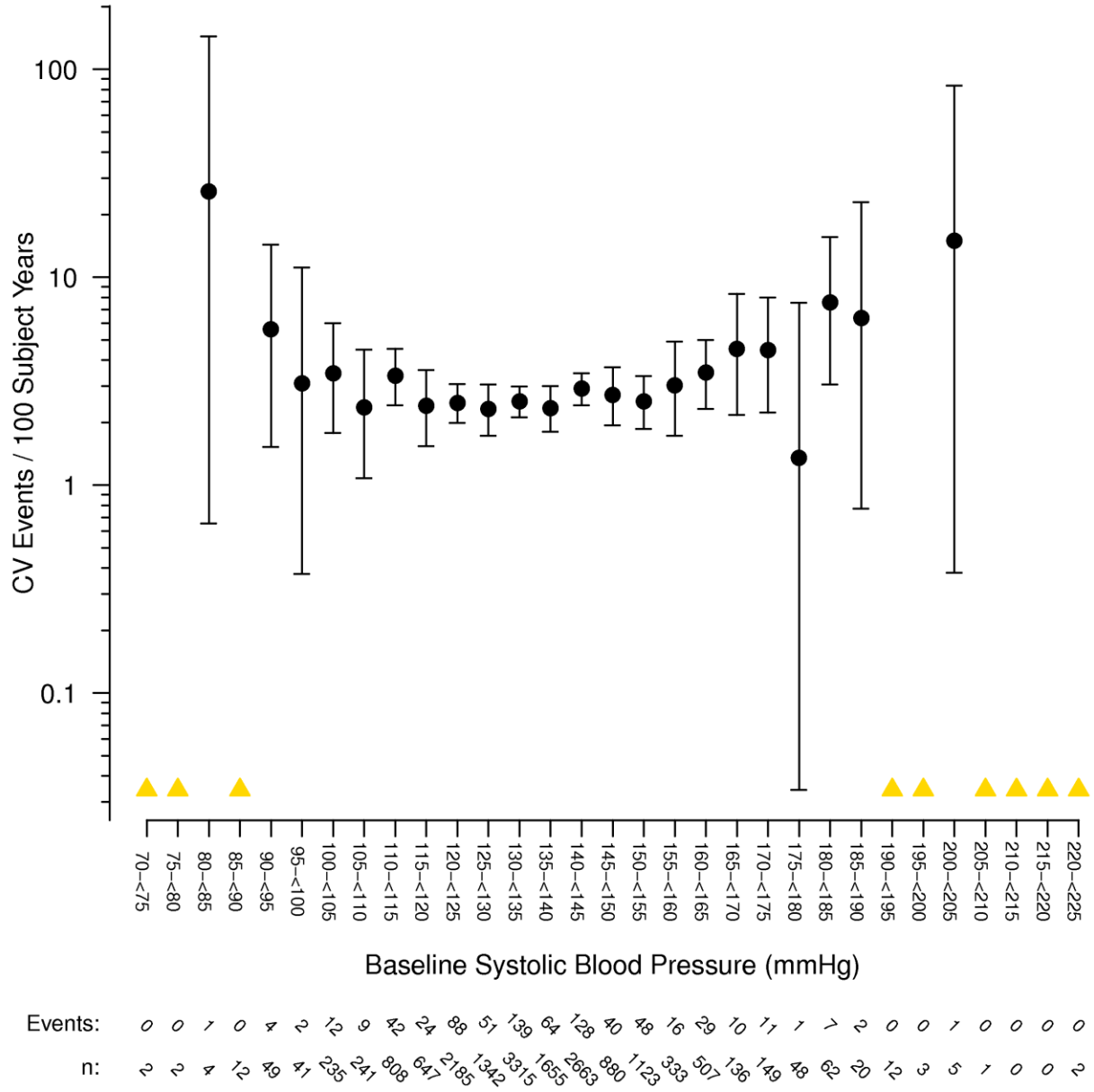

100
10
1
0.1
CV Events / 100 Subject Years
70–<75
75–<80
80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
125–<130
130–<135
135–<140
140–<145
145–<150
150–<155
155–<160
160–<165
165–<170
170–<175
175–<180
180–<185
185–<190
190–<195
195–<200
200–<205
205–<210
210–<215
215–<220
220–<225
Baseline Systolic Blood Pressure (mmHg)
Events: 0 0 1 0 4 2 12 9 42 24 88 51 139 64 128 40 48 16 29 10 11 1 7 2 0 0 1 0 0 0 0
n: 2 2 4 12 49 41 235 241 808 647 2185 1342 3315 1655 2663 880 1123 333 507 136 149 48 62 20 12 3 5 1 0 0 2

Figure S10

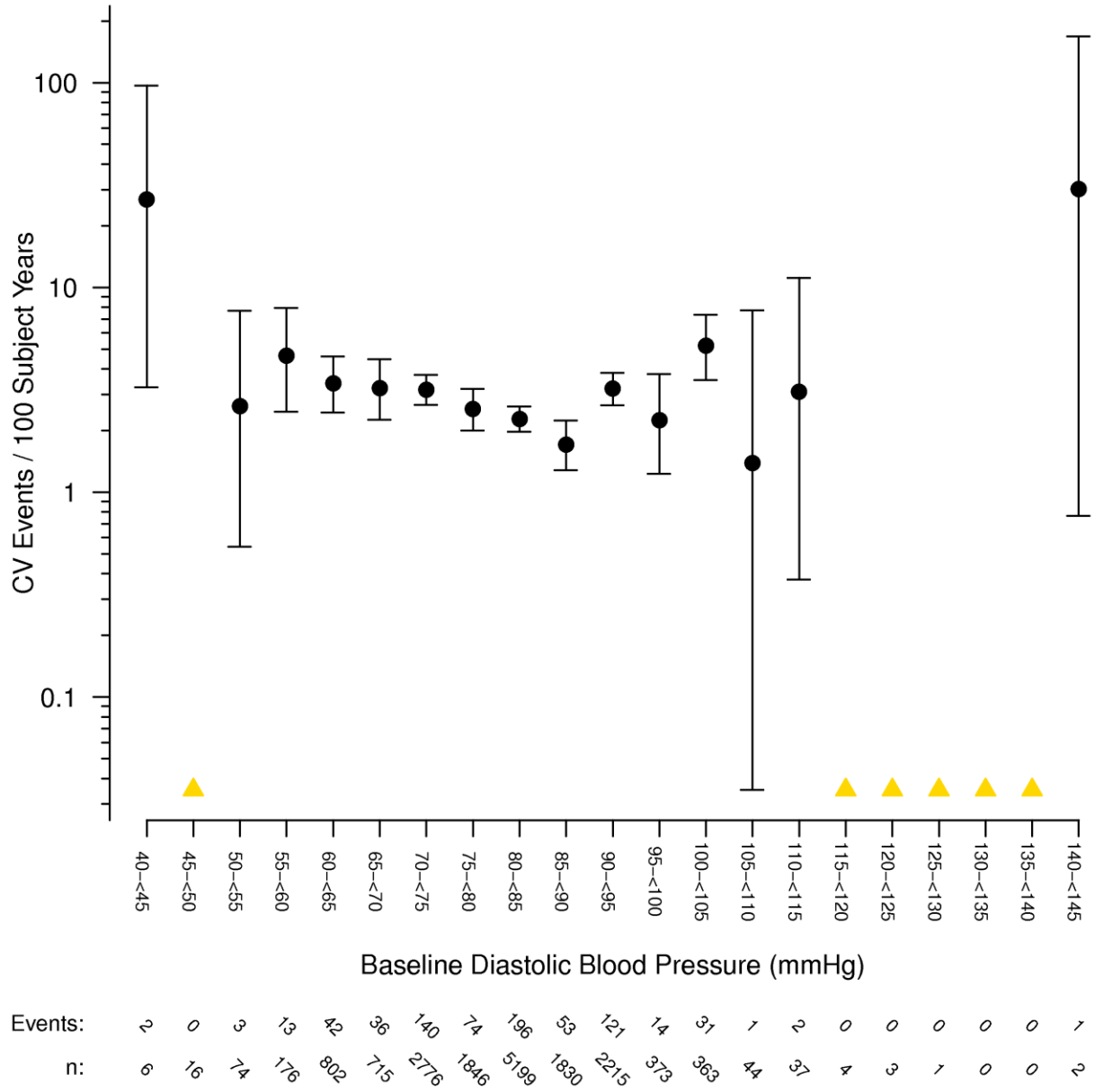

100
10
1
0.1
CV Events / 100 Subject Years
40–<45
45–<50
50–<55
55–<60
60–<65
65–<70
70–<75
75–<80
80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
125–<130
130–<135
135–<140
140–<145
Baseline Diastolic Blood Pressure (mmHg)
Events: 2 0 3 13 42 36 140 74 196 53 121 14 31 1 2 0 0 0 0 0 1
n: 6 16 74 176 802 715 2776 1846 5199 1830 2215 373 363 44 37 4 3 1 0 0 2

Figure S11

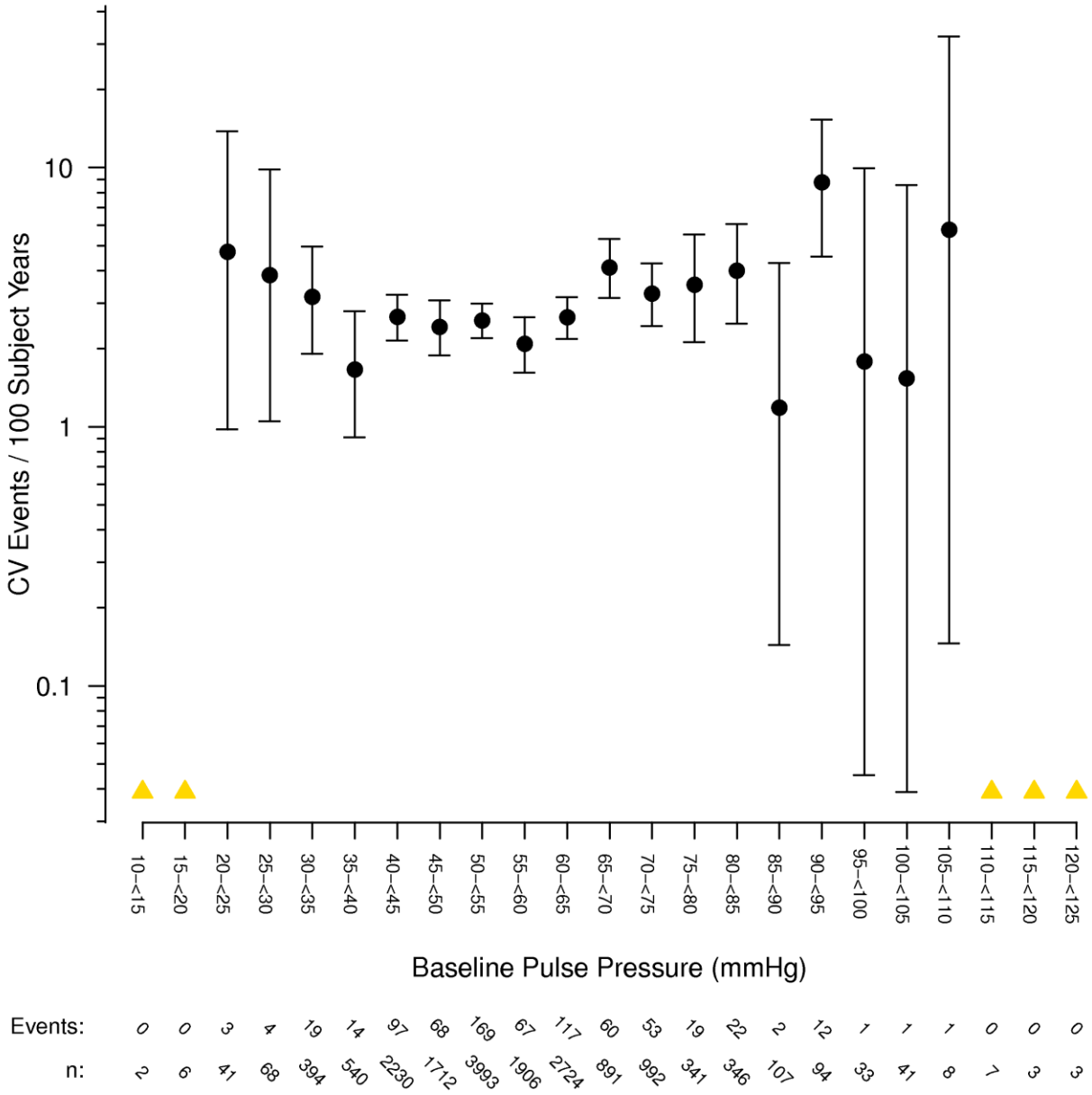
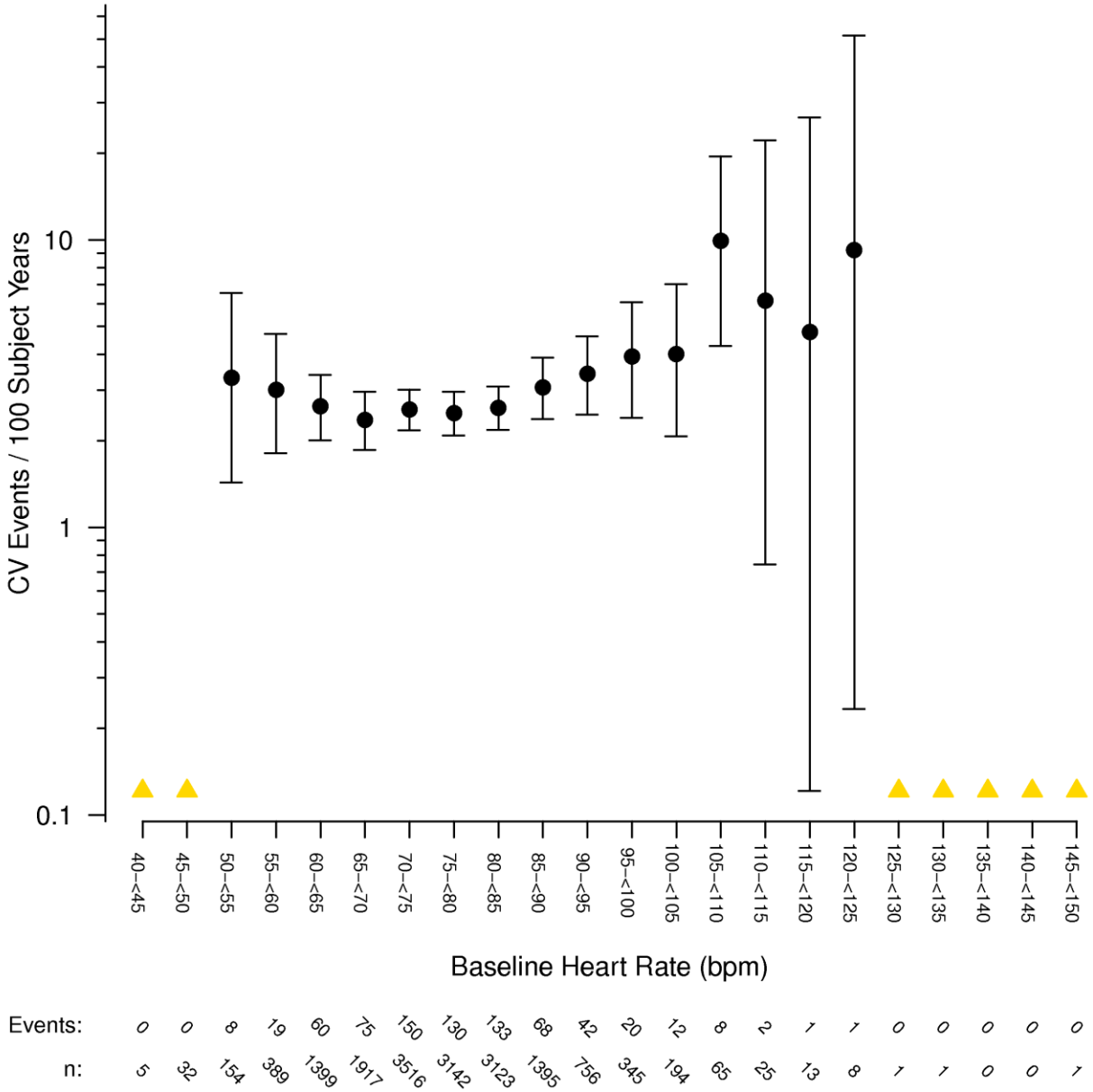

CV Events / 100 Subject Years
10
1
0.1
10–<15
15–<20
20–<25
25–<30
30–<35
35–<40
40–<45
45–<50
50–<55
55–<60
60–<65
65–<70
70–<75
75–<80
80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
Baseline Pulse Pressure (mmHg)
Events: 0 0 3 4 19 14 97 68 169 67 117 60 53 19 22 2 12 1 1 1 0 0 0
n: 2 6 41 68 394 540 2230 1712 3993 1906 2724 891 992 341 346 107 94 33 41 8 1 3 3

Figure S12


CV Events / 100 Subject Years
10
1
0.1
40–<45
45–<50
50–<55
55–<60
60–<65
65–<70
70–<75
75–<80
80–<85
85–<90
90–<95
95–<100
100–<105
105–<110
110–<115
115–<120
120–<125
125–<130
130–<135
135–<140
140–<145
145–<150
Baseline Heart Rate (bpm)
Events: 0 0 8 19 60 75 150 130 133 68 42 20 12 8 2 1 1 0 0 0 0 0
n: 5 32 154 389 1399 1917 3516 3142 3123 1395 756 345 194 65 25 13 8 1 1 0 0 1